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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 2094/1E285-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kevin M. GORMAN, David R. PATTERSON, Jeffrey M. LINNEN and Keming SONG

Serial No.: 09/494,332 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. GOLDBERG

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT MULTIPLEX DETECTION OF HEPATITIS C VIRUS (HCV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND METHOS OF USE THEREOF

RESPONSE TO OFFICE ACTION AND AMENDMENT UNDER 37 C.F.R. 1.111

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Office Action mailed on April 27, 2001 for this application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks. The amendments are made pursuant to the requirements of Rule 121 of the Rules of Practice. Accordingly, Applicants are submitting herewith: (1) a copy of the

amended claims marked up, as required under 37 C.F.R. § 1.121(c)(ii), to show all changes relative to the previous version of each claim and attached hereto at Exhibit Tab A. Applicants also submit herewith, for the Examiner's consideration along with the below remarks:

(2) a copy of the decision by the U.S. Court of Appeals for the Federal Circuit (the "Federal Circuit") for the case of *In re Deuel*, 34 USPQ2d 1240 (Fed. Cir. 1995), attached hereto at Exhibit Tab B;

(3) a copy of the Federal Circuit's decision for the case of *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), attached hereto at Exhibit Tab C; and

(4) a Supplemental Information Disclosure Statement, including Form PTO-1449 with copies of the references cited therein and accompanied by a Search Report from corresponding European patent application no. EP 00 30 0789.

A Petition for Extension of Time is also submitted herewith, accompanied by the appropriate fee and requesting that the time period for responding to the Office Action be extended for **one** month, from **JULY 27, 2001** up to and including **AUGUST 27, 2001**. It is believed that no other fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is due or that a refund is owed for this

application, the Commissioner is hereby authorized and requested to charge any fee(s) due and/or credit any refund(s) owed to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE CLAIMS:

Amend claims 9, 16, 24 and 26, as indicated at Exhibit Tab A, so that the amended claims read as follows:

C1

9. (Amended) A method as defined in claim 1, wherein the HCV and HIV RNA are simultaneously co-detected.

C2

16. (Twice amended) A method for detecting Hepatitis C Virus (HCV) RNA or Human Immunodeficiency Virus (HIV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using RNA derived from said sample and internal positive control (IPC) RNA as a template, at least one reverse transcription primer that will prime reverse transcription of DNA from IPC RNA, at least one reverse transcription primer that will prime reverse transcription of DNA from HCV RNA, and at least one reverse transcription primer that will prime reverse transcription of DNA from HIV RNA to produce reverse transcription products comprising (a) IPC-specific reverse transcription products, (b) HCV-

specific reverse transcription products, (c) HIV-specific reverse transcription products, or (d) any combination of any of the foregoing;

(B) amplifying said reverse-transcription products using one or more pairs of oligonucleotide primers specific for IPC, one or more pairs of oligonucleotide primers specific for the 5' noncoding region of HCV, and one or more pairs of oligonucleotide primers specific for HIV to produce amplification products comprising (a) IPC-specific amplification products, (b) IPC-specific amplification products and HCV-specific amplification products, (c) IPC-specific amplification products and HIV-specific amplification products, or (d) a combination of any of the foregoing;

wherein each of said pairs of oligonucleotide primers specific for IPC comprises:

(1) forward primer 5'-CGCCAGCGTGGACCATCAAGTAGTAA-3' (IPCF1) <SEQ ID NO. 8>, and

(2) reverse primer 5'-CACGATCCTGGAGCAGACACTGAAGA-3' (IPCR1) <SEQ ID NO. 9>;

wherein each of said pairs of oligonucleotide primers specific for HCV comprises:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 10>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 11>; and

wherein each of the pairs of oligonucleotide primers specific for HIV-1 comprises a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

C2

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,

wherein each of the pairs of oligonucleotide primers specific for HIV-2 comprises a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence 5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>; and

(C) detecting said amplification products

wherein detection of IPC-specific amplification products indicates the presence of IPC RNA in said sample, detection of HCV-specific amplification products indicates the presence of HCV RNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV RNA in said

sample, and the detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV RNA and HIV RNA in said sample.

C2

24. (Amended) A method as defined in claim 16, wherein the HCV and HIV RNA are co-detected simultaneously.

C3

26. (Amended) A method as defined in claim 25, further comprising:

(B) detecting said amplification products,

wherein detection of IPC-specific amplification products indicates the presence of IPC DNA in said sample, detection of HCV-specific amplification products indicates the presence of HCV DNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV DNA in said sample, and the detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV DNA and HIV DNA in said sample.

C4

REMARKS

At the outset, Applicants thank Examiners Jeanine Goldberg and Lisa Arthur for the courtesies extended during the telephonic interview with Applicants'

undersigned representative on Wednesday, July 25, 2001. The remarks presented here reflect the content of that interview.

Claims 1-46 are pending in this application. Claims 9, 16, 24 and 26 have been amended to correct typographical errors mentioned in the Office Action. In particular, claims 9 and 24 have been amended to correct the lack of antecedent basis for the term "co-detecting". Claim 16 has been amended to correct the typographical errors noted by the Examiner, and claim 26 has been amended to correctly depend from claim 25. These amendments do not contain new matter and claims 1-46 will remain pending upon the amendments' entry. Entry and consideration of these amendments and remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, HAS BEEN OBVIATED

Claims 9, 16-24, 26-30 and 45 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office Action notes that there are certain typographical errors in claims 9, 16, 24 and 26 that render those claims (and claims depending therefrom) confusing.

The typographical errors have been corrected in the above amendments. Specifically, the Office Action indicates that there is no antecedent basis for the term "co-detecting" recited in claims 9 and 24. Accordingly, those claims have been amended to correct the error by more particularly reciting that the "HCV and HIV RNA are co-detected simultaneously". Claim 16 has been amended

to remove the superfluous "and" between steps (A)(a) and (A)(b). In addition, claim 16 has also been amended, as recommended in the Office Action, to insert a comma between steps (B)(a) and (B)(b). Finally, claim 26 has been amended so that the claim correctly depends from claim 25 rather than from claim 10. Applicants therefore believe that the rejections under 35 U.S.C. § 112, second paragraph, have been obviated and respectfully request that the rejections be withdrawn.

THE REJECTIONS FOR OBVIOUSNESS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The pending claims have also been rejected under 35 U.S.C. § 103(a) as obvious over various references cited in the Office Action. In particular, the claims have been rejected as follows:

(1) Claims 1 and 3-15 have been rejected as obvious over Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 (hereinafter referred to as "Han");

(2) Claims 1 and 3-15 have been rejected as obvious over U.S. Patent No. 6,001,558 issued December 14, 1999 to Backus *et al.* (hereinafter referred to as "Backus");

(3) Claims 1-15 and 43-44 have been rejected as being obvious over (i) Han (*supra*) or (ii) U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* (hereinafter referred to as "Maertens") and Backus (*supra*), in view of (iii) Nedjar *et al.*, "Co-Amplification of Specific Sequences of HCV and HIV-1 Genomes by Using the Polymerase Chain Reaction Assay: A Potential Tool for the Simultaneous Detection of HCV and HIV-1", *J of Virological Methods* 1991, 35:297-304 (hereinafter referred to as "Nedjar");

(4) Claims 31, 33, 35, 37, 39 and 41 have been rejected as being obvious over either Han, or Maertens and/or Backus in view of the Nedjar reference and in further view of Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investiment", *The Scientist* 1995, 9(15):20 (hereinafter referred to as "Ahern").[1]

In making the above rejections, the Examiner has indicated that the cited prior art references of Han and Maertens teach a conserved 5'-UTR of hepatitis C virus (HCV) genome RNA. The Backus reference allegedly relates to oligonucleotides for the amplification and detection of human immunodeficiency virus (HIV) RNA. The Office Action further indicates that Backus may teach certain

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[1] This reference has been cited in the Office Action by the internet web page: www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998.

oligonucleotide primer sequences that are recited in the pending claims. The Nedjar reference allegedly teaches multiplex PCR assays that are capable of simultaneously amplifying and detecting nucleic acids for both HCV and HIV. Finally, the Ahern reference discusses the utility and desirability of kits for biological assays in general, but is not related *per se* to the amplification or detection or any nucleic acid.

The Examiner has acknowledged, in the Office Action, that none of the cited references explicitly teaches the amplification or detection of either HCV or HIV using the particular primer sets recited in the pending claims.[2] Instead, the obviousness rejections appear to be based, at least in part, on the Examiner's contention that the recited primers are actually structural homologs of full length HCV and/or HIV genomic sequences that are described in the cited prior art. The Office Action then concludes, citing the court decision of *In re Deuel*,[3] that the oligonucleotides would be *prima facie* obvious to a person skilled in the art. In response to these arguments, Applicants respectfully submit that the present Office Action fails to establish a *prima facie* case for obviousness under the standards that have been established by the United States Court of Appeals for the Federal Circuit

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[2] See, in particular, at lines 16-17 on page 4; at lines 14-15 on page 7, ¶ 7; at line 20 on page 10; and at lines 5-6 on page 14 of the Office Action.

[3] 51 F.3d 1551, 34 USPQ2d 1210 (Fed. Cir. 1995). For the Examiner's convenience, a copy of the *Deuel* decision (from the U.S. Patents Quarterly reporter) is attached hereto, at Exhibit Tab B. Citations to particular pages in that decision are made here with respect to the attached copy.

(Federal Circuit) and are set forth in the Manual for Patent Examining Procedure (M.P.E.P.).

The legal standard for obviousness under 35 U.S.C. § 103:

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach *all* of the claimed limitations.

The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P. § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Obviousness can only be established by combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. M.P.E.P. § 2143.01. See, also, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art

also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990).

The claimed invention:

Here, the pending claims are directed to particular multiplex PCR assays that are capable of detecting both HCV and HIV nucleic acids in a biological sample, such as in a clinical sample from a patient. As noted by the Examiner, these methods need not necessarily *detect* both HIV and HCV simultaneously in a given sample but may, for example, detect either HCV or HIV RNA alone (*e.g.*, in instances where a patient is infected with one, but not both types of virus). Neverthless, the claimed assays are capable of simultaneously detecting RNA from both types of virus where they are both present in a sample. Accordingly, these methods involve (and the pending claims particularly recite) steps of adding *both* a reverse transcription primer for HCV RNA *and* a reverse transcription primer for HIV RNA. More specifically, the claimed multiplex assays of this invention use primers that are selected from the particular oligonucleotides recited in the pending claims. Applicants have discovered that these specific primer sequences are effective for detecting both types of virus, and may be used simultaneously in a multiplex assay.

to random than both.

The relevant inquiry for
prima facie *obviousness:*

To determine whether these particular assays are *prima facie* obvious under 35 U.S.C. § 103, it must first be shown that a skilled artisan, given knowledge of the HIV and HCV sequences taught in the above-cited references, would have been motivated to select therefrom the particular oligonucleotide sequences recited in the pending claims. Next, it must also be shown that the skilled artisan must be motivated to use those oligonucleotides in combination (*i.e.*, in a multiplex PCR assay). The invention, as a whole, must be apparent to the skilled artisan with a reasonable expectation of success. See, M.P.E.P. § 2143.02. Thus, it is not sufficient to show that a skilled artisan might have a reasonable expectation of success in using *either* the particular HCV-specific primers *or* the particular HIV-specific primers of this invention. It must also be shown that a skilled artisan would reasonable expect that these particular primers can be used *in combination* (*i.e.*, in a single mutliplex assay) to detect HCV and/or HIV nucleic acids in a sample. As explained in detail below, the references cited in the present Office Action do not satisfy this inquiry, and therefore fail to establish a *prima facie* case for obviousness under 35 U.S.C. § 103.

The Deuel decision does not change the requirements for prima facie obviousness under 35 U.S.C. § 103:

The Examiner, in making the obviousness rejections, seems to believe that the particular oligonucleotide sequences of this application are suggested by the prior art because, according to the Office Action, they are structural homologs of the full length HCV or HIV sequences taught in the cited references of Han, Maertens and/or Backus. The Examiner supports this position by citing *In re Deuel* (*supra*), noting that:

> [n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.[4]

However, the *Deuel* court immediately goes on to note that:

> [i]n all of these cases . . . the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art

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[4] *Deuel* (*supra*) at 1214. Cited in the Office Action at pages 4-5, 8, 11 and 14 of the Office Action.

would have suggested making the ***specific*** molecular modifications necessary to achieve the claimed invention.[5]

Thus, the *Deuel* court's decision does not, in any way, establish an exceptional legal standard for *prima facie* obviousness under 35 U.S.C. § 103. Rather, *Deuel* supports the proposition that, for the presently claimed invention to be obvious, a skilled artisan must be motivated, *a priori*, to select the specific primer sequences recited in the pending claims. As noted in the present Office Action, however, none of the cited references suggests these particular modifications to the HCV or HIV genomic sequences taught by Han, Maertens and/or Backus.

Obvious "to try" is not the standard for obviousness under 35 U.S.C. § 103:

At best, the references cited in the Office Action might simply motivate a skilled artisan to try various primer sequences from the HCV and HIV genomic sequences taught by Han, Maertens and/or Backus. Indeed, the skilled artisan may even be motivated to try different combinations of these sequences with the expectation that he or she might find some combination of primers that can be used successfully in a single, multiplex assay to detect HCV and HIV. However, this does not establish a *prima facie* case for obviousness under 35

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[5] *Ibid* (emphasis added).

U.S.C. § 103. To better illustrate this point, the Examiner's attention is directed to the Federal Circuit's decision in *In re O'Farrell*.[6]

In *O'Farrell*, the court considered common circumstances where an invention that may have been "obvious to try" nevertheless is not legally obvious under 35 U.S.C. § 103. In particular, the court notes:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

The *O'Farrell* decision makes it clear that an invention made under such circumstances is not legally obvious under 35 U.S.C. § 103.

The situation here is similar, if not identical, to that described above by the court in *O'Farrell*. In particular, the teachings of the Han and/or Maertens references might, at best, only motivate a skilled artisan to try different oligonucleotides that are complementary to parts of the HCV 5'-UTR sequence taught in those references. Yet, the cited references do not give adequate guidance so that a skilled artisan may determine *which* particular oligonucleotides will

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[6] 853 F.2d 984, 7 USPQ2d 1673 (Fed. Cir. 1988). For the Examiner's convenience, a copy of the *O'Farrell* decision (from the U.S. Patents Quarterly reporter) is attached hereto, at Exhibit Tab C. Citations to particular pages in that decision are made here with respect to the attached copy.

specifically hybridize to the target HCV sequence and not to other sequences that may be present in the biological sample.

Similarly, Backus may describe genomic HIV sequence which might be desirable targets for amplifying and/or detecting HIV nucleic acids in a biological sample. Yet, apart from teaching some specific primer sequences, the reference does not provide guidance that will permit a skilled artisan to select, *a priori*, particular oligonucleotides that will specifically hybridize to and amplify the target HIV sequence in a biological sample.

A skilled artisan would therefore need to experiment and try various oligonucleotides that are complementary to the HCV 5'-UTR sequence(s) taught by Han and Maertens, to determine which particular ones hybridize to those HCV sequences with the required specificity. Similarly, except for whatever oligonucleotide primers are particularly taught by Backus, a skilled artisan would also need to experiment, trying various oligonucleotides complementary to the HIV genomic sequences in that reference to determine which ones actually hybridize to the target HIV sequence(s) with sufficient specificity for detecting HIV in a biological sample. Even if a skilled artisan were to ultimately identify particular oligonucleotide sequences for separately amplifying HCV or HIV in a biological sample, further experimentation would be required to determine which of those primers, if any, may be successfully combined to detect HCV and/or HIV in a single, multiplex PCR assay.

The mere fact that particular sets of HCV and HIV specific oligonucleotide primers recited in the pending claims might eventually be identified through such experimentation does not render the claimed invention legally obvious under 35 U.S.C. § 103, even if such experimentation were routine and not undue. The Federal Circuit's decisions of *Deuel* and *O'Farrell* clearly establish that, for a particular oligonucleotide of this application to be obvious, a skilled artisan must reasonably expect *a priori* that the oligonucleotides will hybridize to the target HCV and HIV sequences with sufficient specificity that they may successfully amplify and detect those nucleic acids in a single, multiplex assay. The skilled artisan must therefore reasonably expect success from the recited sets of oligonucleotide primers without having to engage in any experimentation (routine or otherwise) to identify particular oligonucleotide set that would be suitable for the claimed multiplex PCR assay(s).

No reasonable expectation of success:

As explained in Applicants' previous amendment, a skilled artisan could not have had, *a priori*, the necessary reasonable expectation of success. To demonstrate this point, Applicants once again invite the Examiner's attention to Chapter 15.1, "Enzymatic Amplification of DNA by PCR: Standard Procedures and Optimization" from Ausubel *et al.* (Eds.), *Current Protocols in Molecular Biology*, Vol. 3 (John Wiley & Sons, 1998) pages 15.1.-15.1.15 (hereinafter referred to as

"Ausubel").[7] As previously pointed out by Applicants, the Ausubel reference clearly teaches that primer selection is "unpredictable" and "difficult to trouble shoot."[8]

The Examiner has noted that Ausubel does indicate some guidelines to consider when designing primers for a particular assay. Moreover, the Examiner also indicates that specific optimization kits, computer programs, *etc.* are provided in the art to aid the skilled artisan in primer selection. Yet, the guidelines provided by Ausubel are merely general considerations that may increase the probability that a given primer pair would work. Ausubel further admonishes, however, that primer design (*e.g.*, by computer) "is not foolproof."[9] Thus, even though primer design may be routine, Ausubel clearly establishes that some experimentation will be necessary to identify which particular primers are successful. A skilled artisan cannot reasonably predict, *a priori*, whether a particular primer pair will hybrtidize to a target sequence (*e.g.*, in a biological sample) with the requisite specificity.

In the present instance, moreover, a skilled artisan must not only reasonably expect that the recited oligonucleotide primers will separately amplify HCV and/or HIV target sequences in a biological sample. He or she must also reasonably expect that these primers can successfully amplify for those sequences

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[7] The Ausubel reference was made of record in the Supplemental Information Disclosure Statement filed March 27, 2001 with Applicants' previous amendment. The reference is list as reference 1 in the Form PTO-1449 that accompanied that Information Disclosure Statement.

[8] See, in particular, the right hand column on page 15.1.7 of Ausubel.

[9] See, specifically, the right hand column on page 15.1.9 of Ausubel.

in a multiplex PCR assay. More specifically, a skilled artisan must reasonably expect that the recited HCV-specific primers will successfully amplify and/or detect HCV nucleic acids when combined, in a multiplex assay, with the recited HIV-specific primers and *vice versa*.

The Examiner has argued, in the Office Action, that "multiplexing [PCR] using multiple primers was routine in the art at the time the invention was made"[10] and cites the references of Elnifro[11] and Kimpton[12] to support that argument. Yet, these references actually teach that appropriate primers for multiplex PCR can only be identified through trial and error experimentation. For instance, Kimpton merely examines the effect of varying amplification parameters on the reproducibility and efficiency of a particular multiplex PCR assay, referred to in Kimpton as the quadruplex amplification system. The varied parameters include concentrations of the buffer, primers, deoxynucleotide triphosphates, DNA template and polymerase. Kimpton also varies the number of amplification cycles and the temperature of for both denaturation and annealing. However, the sequence

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[10] See, in particular, on page 17 of the Office Action at lines 14-15.

[11] Elnifro *et al.*, "Multiplex PCR: Optimization and Application in Diagnostic Virology" *Clinical Microbiology Reviews* 2000, 13:559-570. This reference is cited in Form PTO-1449 of the Supplemental Information Disclosure Statement filed on March 27, 2001 with Applicants' previous amendment. A copy of the Elnifro reference was also submitted with that Supplemental Information Disclosure Statement.

[12] Kimpton *et al.*, "Evaluation of an automated DNA profiling system employing multiplex amplification of four terameric STR loci" *Int. J. Leg. Med.* 1994, 106:302-311.

identity of the primers used in this mutliplex PCR assay is *not* varied. Thus, Kimpton in no way supports the proposition that primer sequences in a mutliplex PCR assay can be routinely varied or optimized with any reasonable expectation of success.

The Office Action also cites the Elnifro reference (*supra*), noting that this reference teaches that "the optimization of multiplex PCR should aim to minimize or reduce non-specific interactions"[13] and that "the choice of primers has been shown to be crucial [for multiplex PCR]."[14] Yet, the Elnifro reference makes it abundantly clear that, while the choice of primer sequence is indeed crucial for an effective multiplex PCR assay, there is no way for a skilled artisan to know *a priori* whether a particular primer set will work. Rather, Elnifro explicitly teaches that"

> "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, ***because there are no means to predict the performance characteristics of a selected primer pair*** even among those that satisfy the general parameters of primer design."[15]

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[13] See, in particular, the last line in the right hand column on page 559 through line 1 of the left hand column on page 560 of Elnifro. Cited at lines 18-19 on page 17 of the Office Action.

[14] See, in particular, lines 37-38 in the left hand column on page 560 of Elnifro. Cited on page 17, line 19 of the Office Action.

[15] See, in particular, lines 1-6 in the left hand column on page 560 of Elnifro (emphasis added).

Thus, Elnifro makes it clear that a skilled artisan would only appreciate that a primer set of this invention may be used in a multiplex PCR assay after trial-and-error experimentation. As explained above, however, the use of these primer sets in multiplex PCR is only obvious under 35 U.S.C. § 103 if a skilled artisan could have a reasonable expectation of success *a priori* and without such trial-and-error experimentation, even if the experimentation were not undue.

In summary, the presently claimed methods of this invention are not obvious and, in particular, are not *prima facie* obvious over the references cited in the present Office Action. More specifically, the references of Han and Maertens do not teach or suggest the HCV specific primers recited in the pending claims, and a a skilled artisan could not reasonably expect, *a priori*, that these specific primers may be used to amplify and/or detect HCV nucleic acids in a biological sample. Moreover, given what is taught in the above-discussed prior art, a skilled artisan could not reasonably expect that the particular sets of HCV- and HIV-specific primers recited in the pending claims may be successfully used together in a mutliplex PCR assay. Applicants therefore respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

THE NONSTATUTORY DOUBLE PATENTING REJECTION

Applicants note that claim 1-15 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being

unpatentable over claims 1-64 of copending application serial no. 09/493,353 (hereinafter referred to as "the '353 application"). Because this is a provisional rejection Applicants respectfully decline to respond to the rejection at this time. However, Applicants agree to submit a terminal disclaimer should the Examiner maintain this rejection upon a finding of allowable subject matter in the two applications.

CONCLUSION

For the reasons stated above, Applicants believe that the Examiner's rejections of the pending claims have been overcome and that the claims, as amended, are in condition for allowance. Accordingly, the withdrawal of all objections and rejections, and reconsideration of the application are respectfully requested. The Examiner is invited to contact Applicants' undersigned representative at the below indicated telephone number if she believes it may advance prosecution of this application. An allowance is earnestly sought.

Respectfully submitted,

Dated: August 27, 2001

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